Q What risk factors contribute to *C difficile* diarrhea?

Julia Fashner, MD; Marin Garcia, MD
St. Joseph's Family Medicine Residency Program, South Bend, Ind

Lisa Ribble, PharmD, BCPS
St. Joseph's Pharmacy Residency Program, Mishawaka, Ind

Karen Crowell, MLIS
University of North Carolina, Chapel Hill

ASSISTANT EDITOR

Richard Guthmann, MD, MPH
University of Illinois at Chicago, Illinois Masonic Family Practice Residency Program, Chicago

EVIDENCE-BASED ANSWER

A/ CERTAIN ANTIBIOTICS AND USING 3 OR MORE ANTIBIOTICS AT ONE TIME are associated with *Clostridium difficile*-associated diarrhea (CDAD) (strength of recommendation [SOR]: **B**, 1 heterogeneous systematic review and several good-quality cohort studies).

Hospital risk factors include proximity to other patients with *C difficile* and longer length of stay (SOR: **B**, several good-quality cohort studies).

Patient risk factors include advanced age and comorbid conditions (SOR: **B**, several good-quality cohort studies).

Acid suppression medication is also a risk factor for CDAD (SOR: **B**, 1 heterogeneous systematic review and 2 good-quality cohort studies).

Evidence summary

One systematic review found increased risk of CDAD in patients taking cephalosporins, penicillin, or clindamycin (TABLE 1).[1] A subsequent retrospective cohort investigation of 5619 patients during a CDAD epidemic in Quebec, Canada reported that quinolone antibiotics were most strongly associated with CDAD, whereas other antibiotics posed an intermediate risk.[2]

A prospective cohort study of 101,796 admissions over a 5-year period at a tertiary medical center defined a group of high-risk antibiotics before starting research.[3] They included fluoroquinolones, cephalosporins, intravenous β-lactam/β-lactamase inhibitors, macrolides, clindamycin, and carbapenems. All other antibiotics were considered low risk. High-risk antibiotics were associated with a 3-fold increase in CDAD compared with low-risk drugs (odds ratio [OR]=3.37; 95% confidence interval [CI], 2.64-4.31); number needed to harm [NNH]= 10).[3]

The number of antibiotics is a factor

The number of antibiotics used also may influence the risk of CDAD. A retrospective cohort of 2859 patients from a community hospital found that an increased number of antibiotics was a risk factor for CDAD (OR=1.49; 95% CI, 1.23-1.81; NNH=44).[4] Another retrospective cohort study of 1187 inpatients at a Montreal hospital found 3 or more antibiotics increased the risk (adjusted OR=2.1; 95% CI, 1.3-3.4; NNH=20).[5]

Hospital risks: Proximity to an infected patient, length of stay

A prospective cohort of 252 patients and a retrospective cohort of 1187 patients show that recent hospitalization puts patients at risk for CDAD (TABLE 2).[5,6] Several retrospective cohort studies have shown that patients in close proximity to a *C difficile*–positive patient in the hospital (roommate, neighbor, or subsequent tenant) are at risk for CDAD.[4,7]

Length of hospitalization is also a risk factor.[2] A retrospective cohort study of 2859 patients found that patients with CDAD had spent more time in the hospital—a mean of 19 days compared with 8 days for patients without diarrhea (P<.001).[4] A prospective cohort study of 101,796 admissions reported that the mean length of stay was 15 days (range=8.0-26.0) for CDAD patients compared with 5 days (range=3.0-8.0) for patients without CDAD (P<.001).[3]

CONTINUED

Certain antibiotics, using 3 or more antibiotics at a time, and acid suppression medications are associated with *C difficile* diarrhea.

TABLE 1

Medications associated with *C difficile* diarrhea

Medication	Reported ratio* (95% CI)	NNH†
Antibiotics		
β-Lactam/β-lactamase inhibitor, intraveneous[2]	aHR=1.88 (1.35-2.63)	25
Cephalosporins[1]	RR=2.07 (1.06-6.62)	21
Cephalosporins, first generation[2]	aHR=1.78 (1.28-2.46)	28
Cephalosporins, second generation[2]	aHR=1.89 (1.45-2.46)	25
Cephalosporins, third generation[2]	aHR=1.56 (1.15-2.12)	39
Clindamycin[1]	OR=4.22 (2.11-8.45)	8
Clindamycin[2]	aHR=1.77 (1.06-2.96)	28
Macrolides[2]	aHR=1.65 (1.15-2.39)	33
Penicillins[1]	RR=3.62 (1.28-8.42)	9
Quinolones[2]	aHR=3.44 (2.65-4.47)	10
Acid suppression medication		
Histamine$_2$-receptor antagonist[3]	aOR=1.53 (1.12-2.10)	41
Proton-pump inhibitor daily[3]	aOR=1.74 (1.29-2.18)	30
Proton-pump inhibitor more often than daily[3]	aOR=2.36 (1.79-3.11)	17

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CI, confidence interval; NNH, number needed to harm; OR, odds ratio; RR, risk ratio.

*Because the incidence of *C difficile* diarrhea is low, each reported adjusted hazard ratio or risk ratio is approximately equal to the odds ratio used to calculate number needed to harm.

†Assuming an event rate of 5%.

TABLE 2

Hospital risk factors for *C difficile* diarrhea

Hospital factor	Reported ratio* (95% CI)	NNH†
Length of stay 4-7 vs 1-3 days[2]	HR=4.69 (2.14-10.28)	6
Length of stay 8-14 vs 1-3 days[2]	HR=5.11 (2.34-11.18)	6
Length of stay >15 vs 1-3 days[2]	HR=3.55 (1.53-7.24)	10
Any proximity to CDAD-positive patients[4]	RR=3.34 (2.00-5.57)	10
Admission within previous 3 months[5]	OR=3.0 (1.5-6.0)	11
Admission within previous 30 days[6]	OR= 2.6 (1.13-5.7)	14
CDAD-positive patient in adjacent bed[7]	OR=2.34 (1.56-3.51)	17
Occupying bed of previous CDAD-positive patient[7]	OR-2.33 (1.54-3.52)	17

CDAD, *Clostridium difficile*-associated diarrhea; CI, confidence interval; HR, hazard ratio; NNH, number needed to harm; OR, odds ratio; RR, relative risk.

*Because the incidence of *C difficile* diarrhea is low, each reported hazard ratio or risk ratio is approximately equal to the odds ratio, which was used to calculate number needed to harm.

†Assuming an event rate of 5%.

Patient risk factors: Age and comorbid disease

Two cohort studies found that CDAD patients were about 10 years older than patients without CDAD.[3,8] Among 535 patients in Jerusalem, patients positive for *C difficile* toxin had a mean age of 76±20 years compared with 66±26 years in toxin-negative patients

(*P*<.001).[8] In the previously mentioned study of 101,796 patients, the average age for patients with CDAD was 65.4±16.9 years compared with 56.5±19.9 years for patients without CDAD (*P*<.001).[3]

The patients in this study also showed significant associations between CDAD and comorbid conditions, including myocardial infarction, heart failure, chronic pulmonary disease, peripheral vascular disease, complicated diabetes, fluid and electrolyte disorders, chronic renal failure, cancer, coagulopathy, and methicillin-resistant *Staphylococcus aureus* infection.[3]

Acid suppression therapy is another risk

A systematic review that included a total of 2948 patients in 12 studies (cross-sectional, case-control, and cohort) evaluated acid suppression therapy and found an association between CDAD and use of histamine$_2$-receptor antagonists (H_2RAs) (OR=1.48; 95% CI, 1.06-2.06; NNH=45) and between CDAD and proton-pump inhibitors (PPIs) (OR=2.05; 95% CI, 1.47-2.85; NNH=21).[9] Significant heterogeneity among the studies limited the interpretation of results, however.

The prospective cohort study of 101,796 patients also reported an increased risk of CDAD with H_2RAs and PPIs.[3] The risk of CDAD rose with progression from no acid suppression to H_2RA use to daily PPI use to more frequent PPI use.[3] Another cohort study of 1187 patients found an association between PPIs and CDAD (adjusted OR=2.1; 95% CI, 1.2-3.5).[5]

Using a score to gauge risk

Researchers studying a cohort of 54,226 patients developed a risk score using clinical characteristics associated with CDAD.[10] The patients were older than 18 years, hospitalized longer than 48 hours, and had received broad spectrum antibiotics (intravenous glycopeptides, fluoroquinolones, penicillins, cephalosporins, or carbapenems). When the researchers tested their clinical risk index on a validation cohort of 13,002 patients, they found that increasing scores were significantly associated with increasing risk for *C difficile* colitis (OR=3.31; 95% CI, 2.61-4.91; area under the receiver operating characteristic curve=0.712).[10]

Recommendations

Clinical practice guidelines by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America recommend minimizing the frequency and duration of antibiotics and the total number of antibiotics used.[11] They also suggest private rooms, chlorine cleaning products, and contact precautions (gloves, hand hygiene, and disposable thermometers) to reduce risk.

The authors of the guidelines propose antimicrobial stewardship programs based on the local epidemiology of *C difficile* strains, including restricted use of cephalosporins and clindamycin, except for surgical prophylaxis. JFP

Proximity to other patients with *C difficile* and longer hospital stays increase the risk of infection.

References

1. Thomas C, Stevenson M, Riley TV. Antibiotics and hospital-acquired *Clostridium difficile*-associated diarrhea: a systematic review. *J Antimicrob Chemother*. 2003;51:1339-1350.
2. Pepin J, Saheb N, Coulombe M, et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associate diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis*. 2005;41:1254-1260.
3. Howell MD, Novack V, Grgurich P, et al. Iatrogenic gastric acid suppression and the risk of nosocomial *Clostridium difficile* infection. *Arch Intern Med*. 2010;170:784-790.
4. Chang VT, Nelson K. The role of physical proximity in nosocomial diarrhea. *Clin Infect Dis*. 2000;31:717-722.
5. Dial S, Alrsadi K, Manoukian C, et al. Risk of *Clostridium difficile* diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. *CMAJ*. 2004;171:33-38.
6. Kyne L, Sougioultzis S, McFarland LV, et al. Underlying disease severity as a major risk factor for nosocomial *Clostridium difficile* diarrhea. *Infect Control Hosp Epidemiol*. 2002;23:653-659.
7. Howitt JR, Grace JW, Schaefer MG, et al. *Clostridium difficile*-positive stools: a retrospective identification of risk factors. *Am J Infect Control*. 2008;36:488-491.
8. Raveh D, Rabinowitz B, Breuer GS, et al. Risk factors for *Clostridium difficile* toxin-positive nosocomial diarrhea. *Int J Antimicrob Agents*. 2006;28:231-237.
9. Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol*. 2007;102:2047-2056.
10. Garey KW, Dao-Tran TK, Jiang ZD, et al. A clinical risk index for *Clostridium difficile* infection in hospitalized patients receiving broad-spectrum antibiotics. *J Hosp Infect*. 2008;70:142-147.
11. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31:431-455.